REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 1, 93-96, and 98-114 are pending in the application. Claim 1 is the sole independent claim. Claims 2-92, 97 and 115-125 are cancelled. Claims 2-68 and 115-125 were previously cancelled.

Claims 1, 93, 94, 96, 98, 99, and 105-114 are amended. Claim 1 is amended to incorporate therein the subject matter of claims 91 and 92, which previously depended from claim 1 and are now cancelled. Claims 93, 94, 96, 98, 99, and 105-114 are amended to ensure proper dependency from their antecedent in view of the amendment to claim 1. The foregoing amendments do not add new matter and remain within the elected group and species. Entry and consideration is respectfully sought.

The foregoing amendments are made solely to advance prosecution and without acquiescence to any rejection, and without prejudice or disclaimer of subject matter removed by amendment.

II. The Rejection Under 35 U.S.C. § 103(a)

Applicants note that page 2 of the Office Action asserts that the previously pending claims were directed to a method of [^{11}C] labelling azure B. This is incorrect, as the previously pending claims were directed to a broader genus of phenothiazines, but the issue is now moot in view of the presently pending claims.

A. The rejection

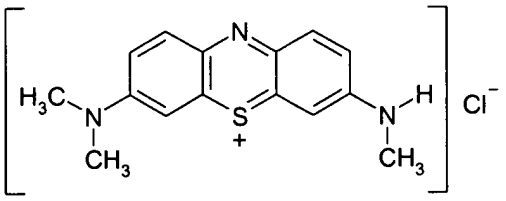
Pages 2-4 of the Office Action reasserts the previous rejection of claims 1 and 63-114 under 35 U.S.C. § 103(a) as allegedly unpatentable over **(a)** Nagren et al. 1998 *J. Labelled Cpd.*

Radiopharm. Vol. XLI, pp. 831-841("Nagren"), disclosing [^{11}C] labelling of compounds using [^{11}C]methyl iodide and [^{11}C]methyl triflate in view of **(b)** Link et al. 1998 *Eur. J. Nucl. Med.* 25(9): 1322-1329 ("Link"), disclosing [^{123}I] and [^{131}I] labelling of methylene blue.

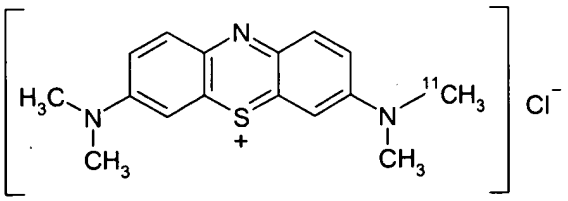
Applicants respectfully traverse this ground of rejection as it might have been applied to pending claims 1, 93-96, and 98-114.

B. Summary of the Claimed Invention

Claim 1 recites a method of [^{11}C]-radiolabelling a phenothiazine compound of the following formula:



said method comprising the step of reacting said phenothiazine compound with [^{11}C]methyl trifluoromethanesulfonate ($CF_3SO_2O^{11}CH_3$) in the presence of a Bronsted base; to give a [^{11}C]-radiolabelled phenothiazine compound of the following formula:



C. The Office has not met its burden of establishing a *prima facie* case

1. Link does not teach N-labelling of an aromatic amine, and differs from the claimed invention in multiple ways

Link describes [^{123}I] and [^{131}] iodination of the aromatic carbons (carbon number 2- and/or 8- on the compound) of methylene blue to generate 2-iodo-methylene blue or 2,8-diiodo methylene blue. This is a classic electrophilic halogenation reaction. By contrast, presently claimed is a method of methylation of the aromatic *amine* of *azure B* to yield *methylene blue*. This reaction proceeds via a nucleophilic S_N2 mechanism. Thus, Link differs from the present claims in the (a) starting materials, (b) product of the reaction (c) site of reaction, and (d) reaction mechanism. Thus, even if Link stood for the concept of radiolabelling methylene blue, as asserted by the examiner, Link does not arrive at radiolabelled methylene blue but a halogenated derivative with chemical properties different from methylene blue.

2. Nagren and the art cited therein do not teach N-labelling of an aromatic amine

Nagren is primarily concerned with the use of [^{11}C]methyl triflate and [^{11}C]methyl iodide to methylate amides and thiols. *See,* e.g., the title "Methylation of amide and thiol functions of ...;" the first sentence of the summary on page 831: "[^{11}C]Methyl triflate was compared with [^{11}C]methyl iodide as a labelled precursor in the synthesis of PET radioligands through ^{11}C-methylation of amide and thiol functions; the last sentence of the summary on page 831: "The results demonstrate that [11C]methyl triflate is compatible with low concentrations of aqueous sodium hydroxide, which enable its use in the preparation of PET radioligands through ^{11}C-methylation of amide and thiol functions;" the introduction at lines 17-18 of page 832: "In a continuation of our previous studies, we have compared [^{11}C]MT with [^{11}C]MI as labelled precursors in the ^{11}C-methylation of amide and thiol functions.

The Examiner has referred to the third full paragraph on page 837 as evidence that Nagren also teaches labelling of amines. This paragraph, which is part of the "Results and Discussion," states:

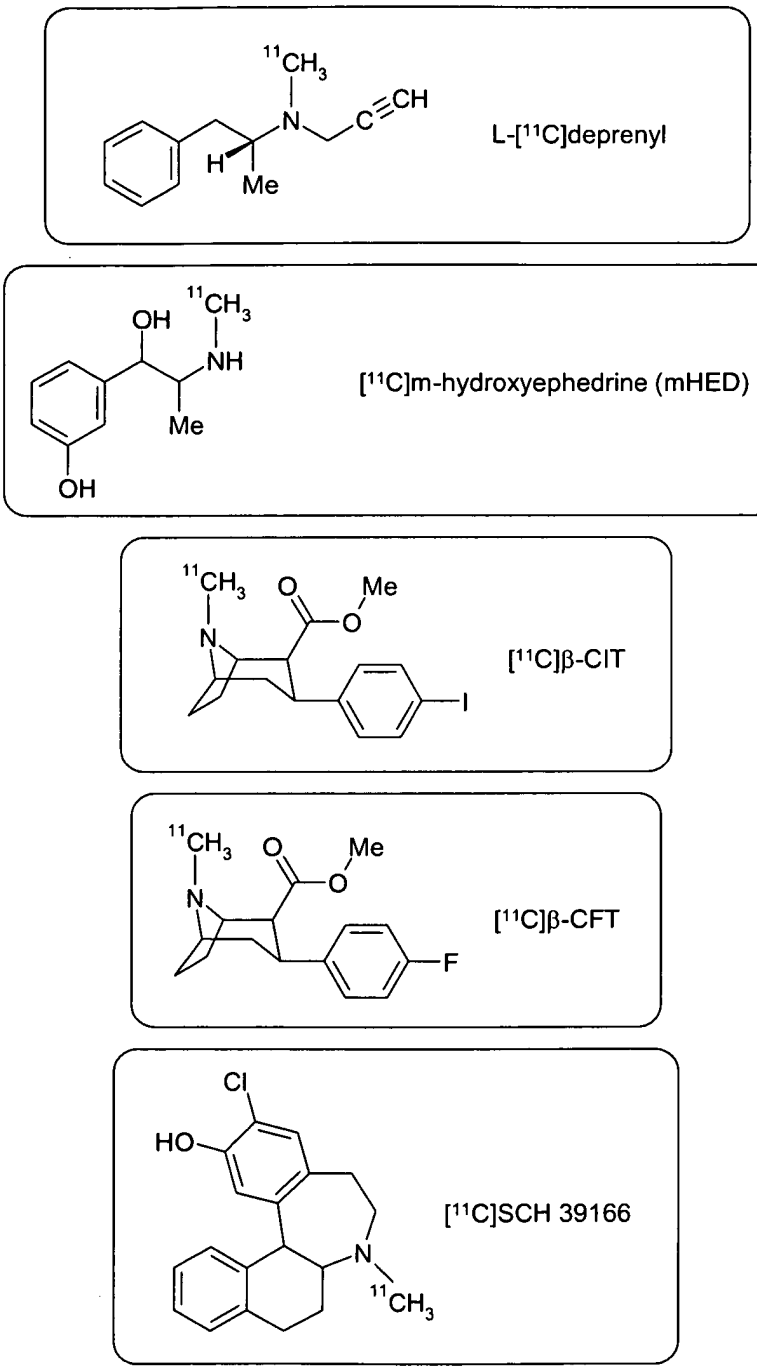
> Preparation of PET radioligands by *N*-methylation of amines is performed using mild reaction conditions *i.e.* methylation of the free base dissolved directly or generated *in situ* from a salt by the use of a mild base such as PMP. The methylation of amide anions require stronger bases such as tetrabutylammonium or sodium hydroxide as commonly used for the preparation of [^{11}C]NMSP (11, 12) or [^{11}C]flumazenil (13, 14). We have used [^{11}C]methyl triflate for the synthesis of [^{11}C]NMSP and [^{11}C]flumazenil and found that a small amount of aqueous sodium hydroxide (1.5 eq.) give high and consistent yields with 1 min heating at 60°C and 0.3-0.5 mg of precursors in 100-300 µL of acetone (Table 1).

It is clear to the skilled person that this paragraph concerns previous methods of N-methylation (using, e.g., [^{11}C]methyl iodide), rather than the compounds under consideration in the document.

Nevertheless, of those documents cited on page 832 of Nagren that do describe N-methylation, including with [^{11}C]methyl triflate, none show N-methylation of an aromatic amine.

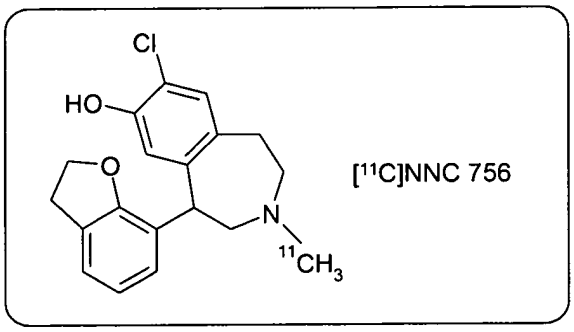
Document (3) Jewett et al., 1992, *Appl. Radiat. Isot.*, Vol. 43, No. 11, pp. 1383-1385, describes the preparation of [^{11}C]methyl triflate, but not its use to [^{11}C]-radiolabel any compound.

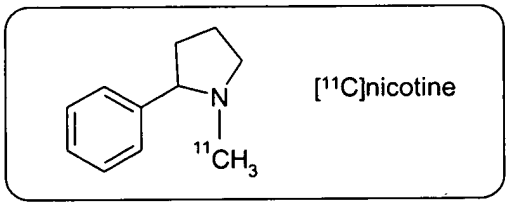
Document (4) Nagren et al., 1995, *Nucl. Med. Biol.*, Vol. 22, No. 2, pp 235-239, describes [^{11}C]-radiolabelling of deprenyl, m-hydroxyephedrine (mHED), β-CIT, β-CFT, SCH 39166, and α-CIT (the less active anomer of β-CIT). All of the compounds are [^{11}C]-labelled at an aliphatic amine group.



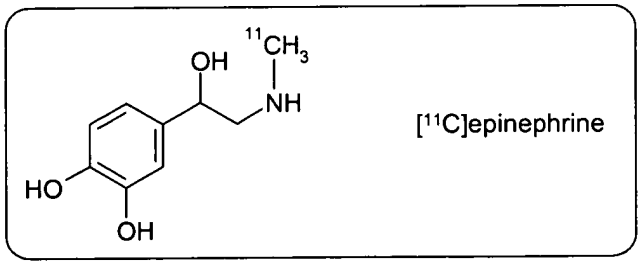
Document (5) Nagren et al., 1995, *Nucl. Med. Biol.,* Vol. 22, No. 8, pp 965-970, describes [^{11}C]-radiolabelling of nicotine and NNC 756 (shown below), and β-CFT, β-CIT,

deprenyl, α-CIT, SCH 39166, deprenyl, and m-hydroxyephedrine (mHED) (which are shown above). All compounds are [^{11}C]-labelled at an aliphatic amine.

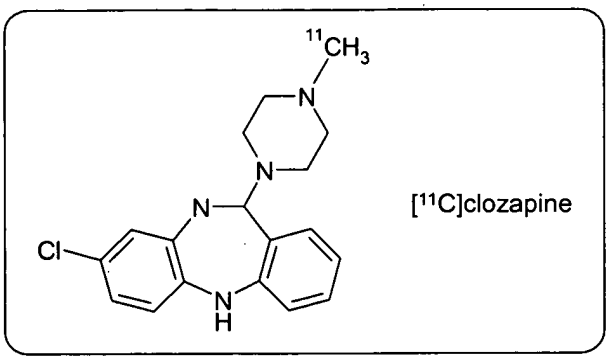




Document (6) Chakraborty et al., 1993, *Nucl. Med. Biol.*, Vol. 20, No. 8, pp. 939-944, describes [^{11}C]-radiolabelling of epinephrine at an aliphatic amine group.

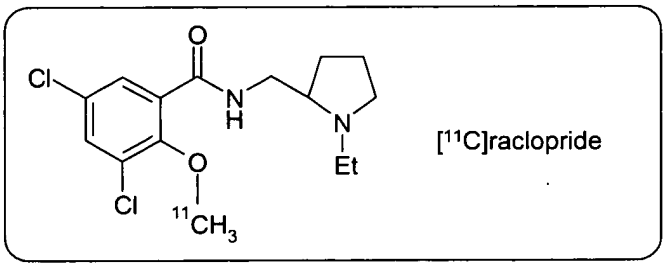


Document (7) Bender et al., 1994, *Nucl. Med. Biol.*, Vol. 21, No. 7, pp 921-925 describes [^{11}C]-radiolabelling of clozapine at an aliphatic amine group.

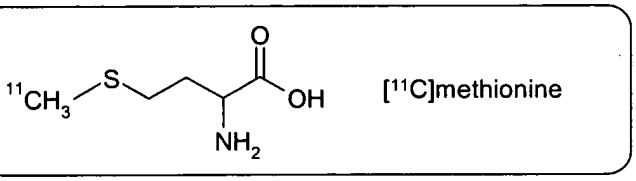


[^{11}C]clozapine

Document (8) Jewett et al., 1994, *J. Lab. Cmpd. Radiopharm.*, Vol. 35, p. 97, describes [^{11}C]-radiolabelling of epinephrine (shown above), raclopride, and methionine (shown below)

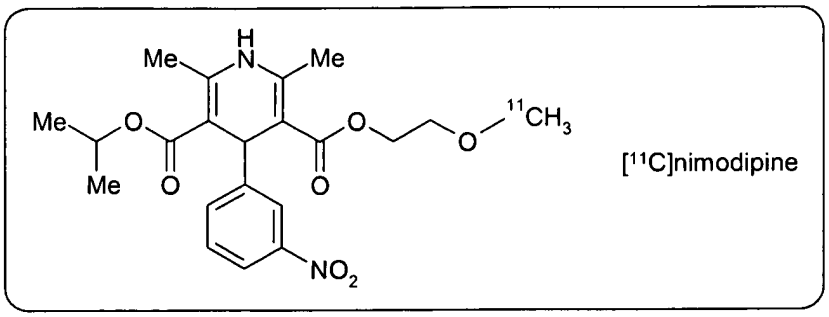


[^{11}C]raclopride

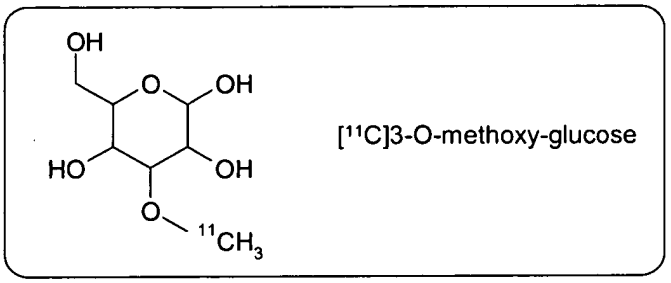


[^{11}C]methionine

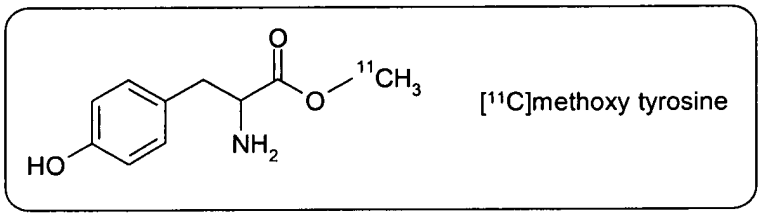
Document(9) Holschbach et al., 1993, *J. Nucl. Med.*, Vol. 34, Abst. No. 268, p. 68P, describes [^{11}C]-radiolabelling of clozapine and methionine (shown above) and, as shown below, nimodipine, 3-O-methyl-glucose, and methoxytyrosine.



[^{11}C]nimodipine

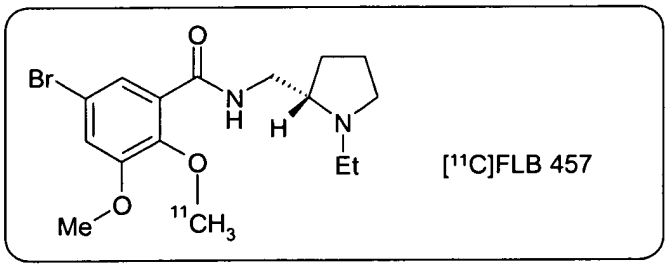


[^{11}C]3-O-methoxy-glucose

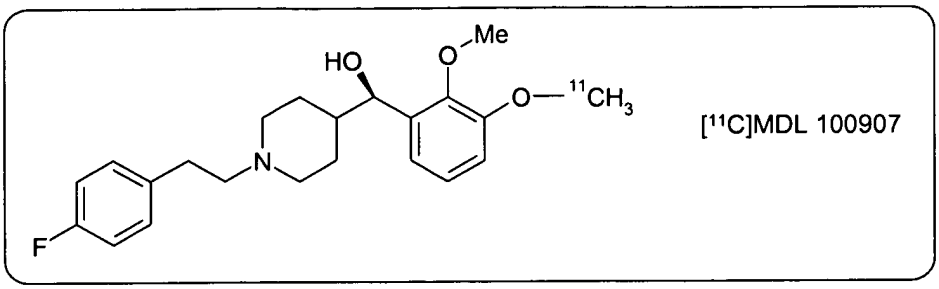


[^{11}C]methoxy tyrosine

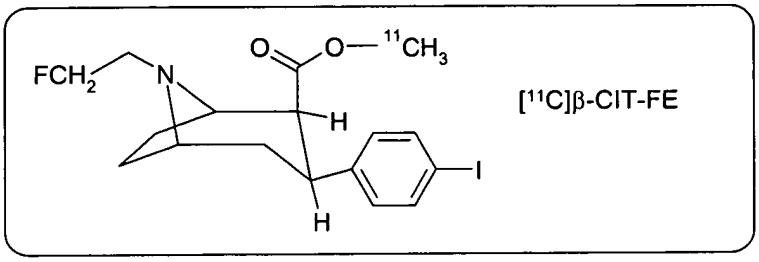
Document (10) Lundkvist et al., 1998, *J. Lab. Cmpd. Radiopharm.*, Vol. XLI, pp. 545,556, describes [^{11}C]-radiolabelling of FLB 457, MDL 100907, β-CIT-FE, and WAY-100635.



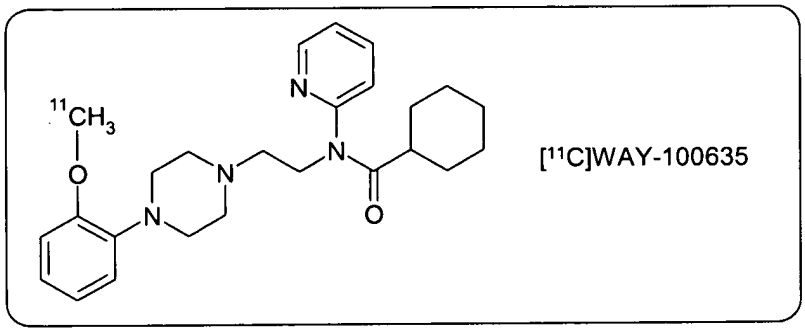
[^{11}C]FLB 457



[11C]MDL 100907



[11C]β-CIT-FE



[11C]WAY-100635

Of those documents that describe labelling at an amine, the amine is attached to an aliphatic group (including primary amines) or is part of an alicyclic ring. None of the foregoing describe [^{11}C]-radiolabelling of an aromatic amine.

The skilled person is well aware of the substantial differences in reactivity between (a) an amine group that is attached to an aliphatic group, or is part of an alicyclic ring and (b) an amine group that is attached to an aromatic ring and therefore stabilized by resonance effects from the adjacent aromatic ring. Such resonance effects are expected to be even greater when conjugated to a series of three aromatic rings, as is the case with the secondary amine in azure B. Accordingly, any prior evidence of a methylation of an amine attached to an aliphatic group, or part of an acyclic ring, does not provide the person of ordinary skill with a reason or suggestion,

or *a prima facie* reasonable expectation of success, in using methyl triflate to methylate the secondary amine in azure B.

3. *No reason or suggestion to combine the references*

a. No reason to combine

Link is concerned with the iodination of an aromatic carbon in methylene blue, and is therefore irrelevant to the labelling of azure B at its secondary amine. Nagren, and its cited references, disclose only the labelling of amines that are linked directly to aliphatic groups, or are part of alicyclic rings, and therefore fail to teach or suggest labelling of the aromatic secondary amine of azure B. These references provide no reason or suggestion for their combination, absent the hindsight provided by Applicants' invention. Moreover, not only is there no reason for the combination asserted, but the references *teach away* from the combination for two independent reasons.

b. Link *teaches away* from the combination

Link describes radiolabelling methylene blue with [^{123}I] or [^{131}I] for use in the detection of melanin in melanoma cells, using gamma camera imaging or positron emission tomography (PET). Between [^{123}I] and [^{131}I], Link preferred the longer-lived isotope [^{131}I], stating that:

> The replacement of ^{123}I ($T_{1/2}$ = 13 h) with much longer-lived ^{131}I ($T_{1/2}$ = 8 days) further improved the clarity and accuracy of the obtained images, and allowed the radioactivity of injected radioiodinated MTB to be reduced by up to 50% (Table 2). The use of ^{131}I instead of ^{123}I also permitted scanning for up to 5 days after the administration of radioiodinated MTB. Since the background from normal organs diminished with the increased time interval between ^{131}I-MTB injection and the imaging of patients, while the level of radioactivity present in melanoma metastases remained stable, the tumour/normal tissue ratios became much greater with time.

Link, page 1327, paragraph bridging the left and right columns (emphasis added). Link identifies the greater benefits of the longer lived ^{131}I isotope a (a) reduced dosage; (b) improved clarity; (c) improved accuracy; (d) more time available for scanning; and (e) improved tumour/normal tissue ratios at longer times. With Link having established the benefit of the longer half-life of ^{131}I ($t_{1/2}$ of 8 days) over ^{123}I ($t_{1/2}$ of 13 hours), the person of ordinary skill would not be motivated to substitute ^{131}I or ^{123}I of Link with ^{11}C in Nagren, because ^{11}C has a dramatically shorter half life of 20.4 minutes - 38 times shorter than that of [^{123}I] and 565 times shorter than that of [^{131}I] – since such a substitution would be expected to lead to loss of the benefits identified by Link. Thus, there is an express reason not to make the combination asserted.

At page 3 of the Action, the Office responds to such arguments by noting that "[t]he claims are drawn to a method of radiolabelling a compound, not comparisons of isotopic half-lives between carbon and iodine." While an accurate characterization of the claimed subject matter, such a statement elides the central issue of the reason or suggestion to combine the references, or to otherwise modify the teachings of the art.

The reason for radiolabelling a particular compound arises from the usefulness of the resulting radiolabelled compound, for example, in diagnosis and/or treatment. Since the usefulness of the radiolabelled compound is directly related to the half-life of the radionuclide, a consideration of the isotopic half-life is critical when considering motivation (and obviousness). For example, in diagnosis and/or treatment, the skilled person would not be motivated to consider using [^{10}C], which has a half-life of about 20 seconds. In the same way, with Link et al. in hand, the skilled person would not be motivated to move away from [^{123}I] and [^{131}I] (with half-lives of 13 hours and 9 days, respectively, and with the practical benefits demonstrated to be associated with those half-lives), towards [^{11}C] (with a very much shorter half-life of 20.4 minutes, and loss of those benefits). In the relevant context therefore, Link's teaching away is relevant to the reason or suggestion to combine the references, or otherwise modify the teachings of the art, to arrive at the presently claimed invention.

It is also important to note that the Office itself attempts to combine Link and Nagren based on the common nexus of radiolabelling for diagnostic or therapeutic reasons (Office Action at page 3). Because the Office asserts this nexus as a reason to combine the references, the same rationale is equally relevant to consider teaching away from such a combination.

c. Base catalyzed demethylation is a known problem in the art and teaches away from the presently claimed method

At the time of filing the present application, it was well known that that methylene blue and azure B are susceptible to base-catalyzed demethylation. As an illustration of this problem, [^{11}C]radiolabelling azure B using [^{11}C]methyl iodide failed to produce radiolabelled methylene blue, with yields less than <0.5%. *See* page 20, lines 12-18 of the description. It is believed that this results from the necessity of using methyl iodide with a base. The person of ordinary skill would therefore avoid the use of basic conditions described by Nagren to label an N-methylated phenothiazine described by Link. As such, the art teaches away from the presently asserted combination, and from claimed invention more generally, which explicitly recites the use of a Bronsted base.

d. Summary: no reason or suggestion to combine

There is no reason or suggestion to combine the references in the manner asserted by the Office and, indeed, the prior art teaches away from such a combination.

4. *No enablement*

A conclusion of obviousness under 35 U.S.C. § 103 requires that the references relied upon be enabling in that they put the public in possession of the claimed invention. MPEP § 2145; *In re Hoeksema*, 399 F.2d 269, 274, 158 USPQ 596, 601 (CCPA 1968) "if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public;" *see also Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776

F.2d 281, 295, 297, 227 USPQ 657, 666, 667 (Fed. Cir. 1985). The requirement for enablement varies with the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Even *if* the prior art of record, as described above, provides some reason or suggestion to attempt methylation of the secondary amine of azure B with methyl triflate (which it does not) it provides no reasonable expectation of success in such an endeavor. This is especially because the art of record does not provide success with methylation of any secondary aromatic amine using methyl triflate, must contend with demethylation side reactions in the presence of base, and must proceed despite clear evidence of failure with methyl iodide. Without such an enabling disclosure, the prior art cannot render obvious the claimed invention.

5. *No prima facie case*

None of the cited references teach [^{11}C]-radiolabelling of an aromatic amine, or the labelling of azure B. Because the combination of cited art cannot provide all elements of the claimed invention, the Office has failed to meet its burden to establish a *prima facie* case of obviousness. Even if all elements were found in the prior art, which they are not, the Office has not shown a reason or suggestion for the asserted combination, especially in view of the teaching away found in the art, or a reasonable expectation of success necessary for the combination to be enabled. For these additional reasons, the Office has not met its burden of setting forth the *prima facie* case. Reconsideration and withdrawal of the rejection is believed proper.

D. Unexpected results

Even if the Office *had* met its burden of establishing a *prima facie* case of obviousness, which it has not, such a determination would be countered by secondary indicia of non-obviousness, such as unexpected results. "This evidence is not just a cumulative or confirmatory

part of the obviousness calculus but constitutes independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008).

As noted above, it was well known the methylene blue and azure B are susceptible to base-catalyzed demethylation. For example, the skilled person would consider it likely that treatment with the conditions taught in Nagren (i.e., 1.5 eq aqueous NaOH, heating for 1 minute at 60°C; see page 638 therein) or the conditions taught in the other documents discussed above, would give rise to undesired demethylation. Consistent with this knowledge, previous attempts to label [^{11}C]radiolabel methylene blue using [^{11}C]methyl iodide failed to produce radiolabelled product (i.e., yields were less than <0.5%. Also consistent with the art-known problem of demethylation, all examples showing the use of [^{11}C]methyl triflate did not target aromatic amines or any compound with an N-methyl group.

The skilled person would believe, therefore, that the application of the prior art methods of [^{11}C]-radiolabelling, when practiced on azure B, would not lead to [^{11}C]-radiolabelled methylene blue. By contrast, the presently claimed successful labelling with methyl triflate is surprising not only in itself, but especially in its high yield and purity.

E. Conclusion

The Office has failed to meet the burden of establishing the prima facie case of obviousness because the cited art fails to teach all elements, provides no motivation to combine, teaches away from the combination asserted by the Office, and does not enable the claimed invention. Even if the burden were met, the unexpected results obtained by the presently claimed method is independent evidence of non-obviousness. For these reasons, the present claims are non-obvious, and withdrawal of the rejection is respectfully sought.

CONCLUSION

All of the stated grounds of rejection have been properly traversed or rendered moot. Thus, the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to credit any overpayment, or charge any additional fees which may be required under 37 C.F.R. §§ 1.16-1.17, or missing, incomplete or incorrect fees, to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition under 37 C.F.R. § 1.136 for such extension and authorize payment of relevant fees from the Deposit Account.

Respectfully submitted,

Date November 8, 2010

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5483
Facsimile: (202) 672-5399

Richard C. Peet
Attorney for Applicants
Registration No. 35,792